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(54) [Title of the Invention]    Method for Treating Ophthalmic Infections With Azithromycin

(57)      [Abstract]

[Problem]    To provide a method for treating infections of the eyes by the topical administration of azithromycin to the eyes.

[Means]      The invention provides a method for treating ophthalmic infections comprising the topical administration of azithromycin, in an amount sufficient for the treatment of ophthalmic infections, to the eyes of animals requiring treatment; and a composition for topical administration directly to the eyes of animals, including humans, which is suitable for the treatment of infections of the eyes, comprising an effective amount of azithromycin in a pharmaceutical vehicle suitable for topical application to the eyes.

## [Claims]

[Claim 1] A method for treating ophthalmic infections, comprising the topical administration of azithromycin, in an amount sufficient for the treatment of ophthalmic infections, to the eyes of animals requiring treatment.

[Claim 2] A method as set forth in Claim 1, wherein the azithromycin is present in a concentration of from 0.1 to 2.5 wt% in a composition comprising a pharmaceutically acceptable topical vehicle.

[Claim 3] A method as set forth in Claim 2, wherein the composition is administered once daily.

[Claim 4] A composition for topical administration directly to the eyes of animals, including humans, said composition being suitable for the treatment of infections of the eyes, and comprising an effective amount of azithromycin in a pharmaceutical vehicle suitable for topical application to the eyes.

[Claim 5] A composition as set forth in Claim 4, wherein the azithromycin is present in a range of from 0.1 to 2.5 wt%.

[Claim 6] A composition as set forth in Claim 4, wherein the azithromycin is present in an amount of 0.5 wt%.

[Claim 7] A composition as set forth in Claim 4, wherein said composition is 0.5% w/w azithromycin dihydrate suspended in an inert, non-allergic, and preservative-free vehicle comprising 55% w/w petrolatum, 42.5% w/w mineral oil, and 2% w/w lanolin.

## [Detailed Description of the Invention]

[0001]

## [Field of Industrial Application]

The present invention relates to a method for treating infections of the eyes by the topical administration of azithromycin to the eyes of animals requiring treatment.

[0002]

## [Prior Art]

Azithromycin is the non-proprietary (generic) name in the United States for 9a-aza-9a-methyl-9-deoxy-9a-homoerythromycin A, which is a broad-spectrum antimicrobial compound derived from erythromycin A. Azithromycin has been disclosed in US Patent 4,474,768 by Bright and in US Patent 4,517,359 by Kobrehel. These patents disclose that azithromycin and certain derivatives thereof have antibacterial properties, making them useful as antibiotics.

[0003]

Azithromycin is usually administered orally in many different formulations such as tablets, capsules, and suspensions for the treatment of antibacterial infections. Prior to the present invention, however, it was not known that azithromycin was effective in topical administration to the eyes. Azithromycin is known to be administered systemically, and to be effective for the treatment of infections of the eyes in humans when administered orally, for example. However, it is also known that antibiotics which are effective when systemically administered are not always effective when topically administered directly to the eyes. It has been reported, for example, that when tetracyclines are

applied to the cornea, they do not penetrate normal uninjured corneas, despite their ability to diffuse into the spinal fluid and intraocular fluids when systemically administered in sufficiently high dosages (Douvas MG, et al, *Arch Ophthalmol.* 46:57 (1951)).

[0004]

[Problems Which the Invention Is Intended to Solve] and

[Means for Solving the Abovementioned Problems] The present invention relates to a method for the treatment of ophthalmic infections comprising the topical administration of azithromycin, in an amount sufficient for the treatment of ophthalmic infections, to the eyes of animals requiring treatment, including humans. As used herein, topical administration means that azithromycin, in the form of a composition comprising azithromycin and a pharmaceutically acceptable topical carrier, is directly applied to the surface of the eye. In a preferred embodiment, the composition is applied directly to the eye in a single daily dose (equivalent to about 5 mg) for 5 days. It should be noted that "single dose" means the amount for one eye.

[0005] The present invention is also intended to provide a composition for topical administration directly to the eyes of animals, including humans, said composition being suitable for the treatment of infections of the eyes, and comprising azithromycin and a pharmaceutical vehicle suitable for topical application to the eyes, wherein the azithromycin in the vehicle is present in a concentration sufficient to cure infections of the eye. In a preferred embodiment, the concentration of azithromycin in the vehicle is a concentration that allows an infection to be cured by a single dose (about 5 mg/eye) of the aforementioned composition when administered once a day for five days. The possibility of topical administration of azithromycin once a day was almost completely unexpected in view of the fact that virtually all drugs are rapidly washed off the precorneal region by lacrimation. Thus, virtually all common topical administration using known antibiotics such as gentamycin and erythromycin requires frequent application as often as 4 to 6 times daily to achieve effective drug levels in the target ocular tissue. By contrast, azithromycin compounds intended for topical use allow relatively high, sustained levels to be reached in ocular tissue, including the cornea, conjunctiva, eyelids, and sclera. The superior penetration of azithromycin into ocular tissue is expected to result in far greater patient compliance by means of the present invention.

[0006] Eye infections which can be treated by topical administration of azithromycin include any that are caused by bacterial species known to be amenable to systemic treatment with azithromycin. The present invention is particularly suitable for the treatment of trachoma, that is, chronic follicular conjunctivitis caused by *Chlamydia trachomatis*, the leading cause of preventable blindness in the world.

[0007] Shown below are the test results of the penetration of azithromycin into various types of ocular tissue in rabbits, as determined 2 and 24 hours following single administration of azithromycin ophthalmic ointment or placebo. In these tests, the ophthalmic ointment prepared by the method described in Example 1 was administered to the left eye, while placebo was administered to the right eye.

[0008]

[Table 1]

Table 1: Concentrations ( $\mu\text{g/g}$  composition<sup>1</sup>) of azithromycin in various types of ocular tissue in rabbits following single administration of azithromycin ophthalmic ointment or placebo

hours after administration	Rabbit 1		Rabbit 2		Rabbit 3	
Ocular tissue	Left <sup>2</sup>	Right <sup>3</sup>	Left	Right	Left	Right
Tears	1.47	<0.01	1.51	0.05	0.84	<0.01
Nictitating membrane	4.93	0.03	7.24	0.03	3.12	0.02
Bulbar conjunctiva	1.71	0.03	2.45	0.06	4.46	0.16
Aqueous humor	0.08	<0.01	0.13	<0.01	0.13	<0.01
Cornea	24.0	0.10	30.8	0.05	#	0.02
Lens	0.01	<0.01	0.01	<0.01	0.04	<0.01
Vitreous humor	<0.01	<0.01	0.06	<0.01	0.02	<0.01
Iris/ciliary body	#	0.02	0.52	0.09	0.52	0.23
Retina/conjunctival vessels	0.08	0.02	0.63	0.03	0.20	0.01
Sclera	0.58	0.01	1.49	0.02	1.69	0.02
Eyelid/palpebral conjunctiva	10.7	0.05	10.5	0.24	14.3	0.14
Lacrimal gland	##	##	0.04	##	0.12	##

hours after administration	Rabbit 4		Rabbit 5		Rabbit 6	
Ocular tissue	Left <sup>2</sup>	Right <sup>3</sup>	Left	Right	Left	Right
Tears	<0.01	0.01	1.26	<0.01	0.31	<0.01
Nictitating membrane	0.79	0.04	1.24	0.04	1.26	0.03
Bulbar conjunctiva	1.82	0.02	0.82	0.02	0.45	0.02
Aqueous humor	0.08	<0.01	0.04	<0.01	0.03	<0.01
Cornea	47.9	0.18	31.6	0.06	7.63	0.01
Lens	0.04	<0.01	0.02	0.03	0.03	<0.01
Vitreous humor	0.02	<0.01	0.01	<0.01	0.02	0.02
Iris/ciliary body	1.83	0.06	0.40	0.05	0.87	0.67
Retina/conjunctival vessels	1.15	<0.01	0.34	0.11	0.75	0.02
Sclera	1.14	0.01	0.52	0.01	0.83	0.02
Eyelid/palpebral conjunctiva	4.78	0.03	4.15	0.05	5.95	0.04
Lacrimal gland	0.16	0.07	0.08	0.08	0.14	##

1: The quantifiable threshold in this test was  $\pm 0.01 \mu\text{g}$  azithromycin/g.

2: The left eye was treated with 0.1 g of 0.5% azithromycin ointment.

3: The right eye was treated with 0.1 g of placebo ointment.

#: tissue missed during treatment.

##: tissue not collected.

[0009]

[Embodiments of the Invention] The term "azithromycin" includes pharmaceutically acceptable salts thereof, anhydrous forms, and hydrated forms. The azithromycin is preferably present in the form of a dihydrate, as disclosed, for example, in European Patent Application 0298650A2 and pending US Patent Application 07/994,040 filed on December 21, 1992 (these patent applications are incorporated herein by reference).

[0010] The composition of the present invention (occasionally referred to as "formulation" herein) comprises azithromycin and a pharmaceutically acceptable vehicle suitable for topical application to the eyes. The azithromycin (calculated using the dihydrate) is typically present in the aforementioned composition in a concentration of between 0.1 and 2.5% (w/w), and usually between 0.2 and 2.0 wt%<sub>m</sub> [sic], based on the weight of the composition. The concentration is preferably 0.5 wt%.

[0011] The composition may contain a preservative if needed, but preferably contains no preservatives. Such compositions may optionally include surfactants, thickeners, buffers, sodium chloride, and water to form sterile ophthalmic aqueous solutions and suspensions. To prepare a sterile ophthalmic ointment formulation, the azithromycin is combined with a suitable vehicle such as a mineral oil, liquid lanolin, or white petrolatum. A sterile ophthalmic gel formulation containing azithromycin can be prepared by suspending the azithromycin in a hydrophilic base, prepared according to published formulations for similar ophthalmic preparations, from a combination of, for example, carboxyvinyl polymers commercially available under the label of the Carbopol trademark (registered trademark by B. F. Company [sic] for a series of such polymers).

[0012] Azithromycin can also be prepared in the form of an isotonic saline ophthalmic solution using glycerine as [missing text]. A preservative can be optionally included as an adjuvant. Such ophthalmic solutions also contain pharmaceutically acceptable buffers, typically combinations of boric acid and sodium borate, sufficient to maintain a solution pH of 7 to 8.

[0013] A preferred composition is 0.5% w/w azithromycin dihydrate in an inert, non-allergic, and preservative-free vehicle comprising 55% w/w petrolatum, 42.5% w/w mineral oil, and 2% w/w lanolin.

[0014] The present invention is further disclosed below by means of the following non-limiting examples. In the following examples, "water" means sterile water suitable for use as injection water.

[End of material requested for translation]